Executive Summary

Modern chemical warfare began in 1915 with the use of chlorine by Germany in a large-scale attack against the Allies near Ypres, Belgium. During World War I, almost 100,000 deaths and more than 1 million casualties were caused by the use of chemical warfare (CW) agents, such as chlorine, phosgene, and sulfur mustard. The 1925 Geneva Protocol prohibited the use of chemical and biological weapons but did not address their development, production, and storage. Unfortunately, the use of CW agents continued: they were used by Italy against Ethiopia (1935-1936), by Japan against China (1939-1944), and by Iraq against Iran and against its own Kurdish population (1983-1988). The threat of chemical warfare by Iraq was reported during the Persian Gulf War in 1991.

CW agents are generally designed to be used on opposing military forces to produce death or incapacitation. When they are used in military attacks, they are potential contaminants of field drinking-water supplies. CW agents that could appear in military field water and that are of particular concern to the Army are 3-quinuclidinyl benzilate (BZ), organophosphorus nerve agents (GA, GB, GD, and VX), sulfur mustard agents (HD, THD, and HT), T-2 toxin (a fungal metabolite), lewisite (an arsenical vesicant), and cyanide.

Military standards for field drinking-water supplies exist for all the CW agents listed above except T-2 toxin; however, comprehensive re-

view of the standards has not been performed since the 1960s. Therefore, the U.S. Army Office of the Surgeon General is updating these standards to assist the Army in protecting the health and performance of military personnel potentially exposed to toxic concentrations of CW agents in field drinking water during combat. The Army, in collaboration with the Lawrence Livermore National Laboratory, performed the following: (1) reviewed and assessed the potential adverse health effects associated with ingestion of selected CW agents, (2) defined criteria for establishing revised field drinking-water standards for each of these agents, and (3) recommended revision, as needed, to the current field drinking-water standards.

The Army requested that the National Research Council (NRC) review the toxicity of selected CW agents and assess the adequacy of its proposed field drinking-water standards. The NRC was asked to take into consideration the Army's assumptions concerning duration and amount of consumption of contaminated field drinking water. To develop consistent field drinking-water guidelines for the CW agents, the Army assumes the following regarding water-consumption rates and exposure periods:

- The maximum individual daily amount of drinking water required by military personnel to remain combat-effective ranges from 5 to 15 liters (L)/day, depending on the climate, season, and intensity of work.
- Military personnel are not expected to be exposed to CW agents for more than 7 days. Therefore, short-term (7-day) field drinking-water standards are recommended for all the CW agents.

The Army's proposed standards for short-term consumption of drinking water contaminated with CW agents are not intended for application to civilian populations and do not represent standards for drinking water treated at fixed or permanent military installations. These proposed standards assume some degree of water treatment, either by individual disinfection (iodine tablets, chlorine ampules, or boiling) or by portable devices. Some soldier-performance degradation, casualties from toxic-substance exposure, and reduced combat efficiency are to be expected in these situations.

The NRC assigned this study to the Committee on Toxicology (COT),

which organized the Subcommittee on Guidelines for Military Field Drinking-Water Quality to evaluate the toxicity of 3-quinuclidinyl benzilate, organophosphorus nerve agents, sulfur mustard agents, T-2 toxin, lewisite, and cyanide.

This report presents the subcommittee's evaluations of the Army's proposed standards. The report also presents the subcommittee's recommendations for preventing adverse health effects in military personnel exposed to CW agents in field drinking water and for improving the toxicity data base for these CW agents. It should be noted that the intent of this report was not to review the toxicity of the CW agents in detail but to determine the adequacy of the Army's proposed field drinking-water standards. For greater detail on the toxicity of the CW agents, the reader is referred to the reports of the Lawrence Livermore National Laboratory and the U.S. Army.[1]

The subcommittee's recommendations on acceptable exposure levels of CW agents in field drinking water for military personnel are referred to as "guidelines" rather than "standards." The subcommittee believes that the use of the term "guidelines" provides the necessary flexibility to

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[1]Lawrence Livermore National Laboratory. February 1988. Evaluation of Military Field-Water Quality, Vol. 4, Part 1, J.I. Daniels, ed. Publ. No. AD UCRL-21008. Report prepared for the U.S. Army Medical Research and Development Command, Fort Detrick, Frederick, Md.

Lawrence Livermore National Laboratory. January 1990. Evaluation of Military Field-Water Quality, Vol. 4, Part 2, J.I. Daniels, ed. Publ. No. AD UCRL-21008. Report prepared for the U.S. Army Medical Research and Development Command, Fort Detrick, Frederick, Md.

Lawrence Livermore National Laboratory. May 1990. Evaluation of Military Field-Water Quality, Vol. 1, Executive Summary, J.I. Daniels and G.M. Gallegos, eds. Publ. No. AD UCRL-21008. Report prepared for the U.S. Army Medical Research and Development Command, Fort Detrick, Frederick, Md.

U.S. Army. 1988. Recommended Field Drinking Water Criteria for Chemical Agent Sulfur Mustard. Technical Report 8816. U.S. Army Biomedical Research and Development Laboratory, Fort Detrick, Frederick, Md.

U.S. Army. 1990. Field-Water Quality Standards for BZ. Technical Report 9001. U.S. Army Biomedical Research and Development Laboratory, Fort Detrick, Frederick, Md.

field commanders who must weigh the application of exposure recommendations against the need for adequate hydration, combat readiness, and mission success. The term "standards" implies a regulatory limit that cannot be exceeded.

The subcommittee reviewed the Army's criteria for developing field drinking-water standards and generally agrees with the criteria. Therefore, the subcommittee did not develop its own criteria for establishing guidelines for CW agents in military field drinking water.

The toxicity of the CW agents and the adequacy of the Army's proposed field drinking-water standards are summarized in the following sections; the subcommittee-recommended field drinking-water guidelines for CW agents are also presented.

The subcommittee judged that acute adverse health effects and performance-degrading effects among military personnel are the most relevant toxicity end points for deriving field drinking-water guidelines for short-term exposures of 7 days or less. The possibility of carcinogenic effects from exposures of less than 7 days is remote. However, the report calls attention to data on the potential carcinogenicity or genotoxicity whenever it is applicable.

The subcommittee notes that the physical reactions, such as hydrolysis or oxidation, and the poor solubility of most of the CW agents all reduce the potential for exposure via ingestion. The exposure guidelines do not take into account the potential reduction in exposure due to the physical reactions and poor solubility and therefore are even more protective of health.

AGENT BZ

Agent BZ (3-quinuclidinyl benzilate) produces profound hallucinogenic effects in humans. Production of BZ was terminated in 1964 because of the realization that its effects on front-line troops would be varied and unpredictable (thus the term "buzz" or Agent BZ). Toxic effects from oral exposure to BZ include rapid pulse, dry mouth, blurred vision, poor coordination, stupor, confusion, hallucinations, paresthesia of the legs, weakness, speech difficulties, and tremors of the face and arms.

Sufficient human toxicity data are available for BZ to set standards for field drinking water. In one study, heart rate, blood pressure, disorientation, and delirium were evaluated following oral administration of BZ to

healthy male volunteers. The no-observed-adverse-effect level (NOAEL) for BZ was estimated to be 0.5 microgram per kilogram (μg/kg) of body weight. For a person weighing 70 kg, the NOAEL is equivalent to 35 μg/day. Based on a NOAEL of 35 μg/day, the Army recommended field drinking-water standards for BZ of 2.3 μg/L and 7 μg/L, assuming a water consumption of 15 L/day and 5 L/day, respectively. The subcommittee is in agreement with the Army's proposed standards. Therefore, the subcommittee's recommended field drinking-water guidelines for BZ are the same as the Army's proposed standards.

ORGANOPHOSPHORUS NERVE AGENTS

Organophosphorus nerve agents have been used as CW agents for over 50 years. Those of current concern are tabun (Agent GA), sarin (Agent GB), soman (Agent GD), and Agent VX. These synthetic chemicals are among the most acutely toxic substances known.

Symptoms and signs of acute toxicity of organophosphorus nerve agents include excessive bronchial, salivary, ocular, and intestinal secretions. Other symptoms and signs are sweating, bronchospasm, diarrhea, slow heart beat, muscle fasciculation, twitching, weakness, paralysis, loss of consciousness, tension, anxiety, restlessness, convulsion, and depression of central respiratory drive.

Organophosphorus nerve agents bind the enzyme acetylcholinesterase (AChE) and inactivate it, thereby allowing accumulation of large amounts of acetylcholine at neural synapses and neuroeffector junctions. Toxic effects of organophosphorus nerve agents have been largely attributed to inhibition of AChE. Even though there is a relationship between organophosphate toxicity and AChE inhibition, this relationship is not sufficiently precise to predict the risk to humans exposed at low concentrations. There is a need to augment enzyme-inhibition data with other measures of chemical exposure to develop more accurate health guidelines. Such measures are currently unavailable; thus, the use of AChE inhibition data is the only available alternative.

The Army's proposed standards for organophosphorus nerve agents, based on modeled estimates of 50% AChE inhibition following GD exposure, are 4 μg/L and 12 μg/L for a water consumption of 15 L/day and 5 L/day, respectively. The subcommittee, however, disagrees with

the Army's approach of using 50% AChE inhibition as the basis for the standards. Clinical signs and symptoms of toxicity of organophosphorus nerve agents have been reported to occur in some individuals at 50% inhibition of AChE. In addition, a 50% inhibition of AChE might be associated with performance degradation in healthy adults. To accommodate for the biological variability inherent in red-blood-cell acetylcholine measurements (up to a 2-fold difference) and the possibility of confounding effects from exposure to other anticholinesterase chemicals, to assure against decreased battlefield performance, and to protect previously sensitized individuals, the subcommittee selected an AChE inhibition level of 25% as a definite NOAEL. It should be noted that the lowest level of statistical reliability in measuring AChE changes is approximately 20%; changes that are less than 20% cannot be detected reliably.

Based on the available data, the subcommittee recommends that the 25% AChE inhibition level be used as the basis for the field drinking-water guidelines for organophosphorus nerve agents and recommends the following guidelines for the organophosphorus nerve agents: GA, 22.5 μg/L and 70.0 μg/L; GB, 4.6 and 13.8 μg/L; GD, 2.0 and 6.0 μg/L; and VX, 2.5 and 7.5 μg/L—assuming a water consumption of 15 and 5 L/day, respectively. The subcommittee concludes that these guidelines are appropriate until the results of future research indicate that 25% AChE inhibition is inadequate or overly conservative..

SULFUR MUSTARD AGENTS

Three sulfur mustard agents are found in CW arsenals: Agent HD (distilled sulfur mustard), Agent THD (HD to which an acryloid copolymer (T) is added as a thickener to increase its viscosity), and Agent HT (a combination of 60% HD and 40% T, which lowers the freezing point of the mixture).

The sulfur mustard agents are vesicants, causing blistering on exposed skin and mucous membranes, and are lethal at high doses. No controlled studies on human ingestion of sulfur mustard agents exist in the literature. Gastrointestinal irritation is considered the primary toxic effect following ingestion of low concentrations of sulfur mustard compounds in drinking water.

The literature on the toxicity of sulfur mustard agents primarily con-

tains information on the toxicity of HD. The subcommittee assumed that the toxicity of the other sulfur mustard agents—THD and HT—is similar to that of HD.

In a subchronic-toxicity study, rats were administered HD by gavage at doses ranging from 0.0033 to 0.3 mg/kg of body weight. Epithelial hyperplasia of the forestomach was observed in the 0.3-mg/kg group. The no-observed-effect level (NOEL) was estimated to be 0.1 mg/kg/day. Based on that NOEL in rats, the subcommittee recommends field drinking-water guidelines for HD of 47 μg/L and 140 μg/L, assuming a water consumption of 15 L/day and 5 L/day, respectively. The subcommittee's recommended guidelines for sulfur mustard are the same as the Army's proposed standards.

For an exposure lasting 7 days in a lifetime of a person, the increased risk of cancer from exposure to HD at 140 μg/L, assuming a water consumption of 5 L/day, is calculated to be 4.1×10^{-5}. However, given the limited solubility of HD in water, the resulting dose and thus the actual risk might be considerably less.

It is not known how much excess chlorination or iodination is needed to degrade various concentrations of sulfur mustard in raw water. It is possible that disinfectant materials currently used to treat field drinking water substantially reduce concentrations of sulfur mustard. The subcommittee recommends that this approach for reducing sulfur mustard in water be further investigated.

T-2 TOXIN

T-2 toxin is a mycotoxin and a metabolite of several species of fungi. T-2 toxin has been implicated as a CW agent in Southeast Asia and Afghanistan. Data on the toxicity of T-2 toxin in animals and humans are limited. Diacetoxyscirpenol (DAS)—also a mycotoxin—is structurally similar to T-2 toxin, and the toxicity data on DAS are substantial because of its use as an antineoplastic drug. Although the data on T-2 toxin in humans are limited, they do indicate that the toxic effects of T-2 toxin are similar to those of DAS. Therefore, DAS is used as a surrogate for T-2 toxin. DAS has been administered in 5-day clinical trials for treatment of cancer in patients who have not responded to other forms of therapy. The most common toxic effects of DAS in cancer patients are

nausea and vomiting. Less common effects are myelosuppression, hypotension, diarrhea, central nervous system dysfunction, and fever and chills. The mechanism through which DAS and T-2 toxin cause toxicity is through the inhibition of protein synthesis.

The Army's proposed field drinking-water standards for T-2 toxin are based on a NOEL of 2.6 μg/kg of body weight per day for DAS in clinical trials. Adjustments were made for the time difference between the 7-day field conditions and the 5-day clinical trials. The subcommittee concludes that the Army's proposed standards of 8.7 μg/L for a water consumption of 15 L/day and 26 μg/L for a water consumption of 5 L/day are appropriate. The subcommittee's recommended field drinking-water guidelines for T-2 toxin are the same as the Army's proposed standards.

The current field-test kit for detecting T-2 toxin in water has a detection limit of 470 μg/L, which is above the field drinking-water guidelines of 8.7 or 26 μg/L recommended by the subcommittee. Therefore, the subcommittee recommends that a field-test kit capable of detecting T-2 toxin at or below the guideline concentrations be developed and made available to soldiers.

LEWISITE

Lewisite is an outdated organoarsenical CW agent. However, it might still be encountered on the battlefield. On contact with the skin or mucous membranes, it causes an intense inflammatory reaction and produces burns and blistering. Lewisite is also a lung irritant and a systemic poison.

Despite the relative longevity of lewisite as a CW agent, the available toxicological data on human and animal exposure are sparse. No human data are available relating to ingestion of lewisite. However, substantial human data are available on the health effects of trivalent arsenic, which is the form of arsenic present in lewisite. Ingestion of arsenic causes gastrointestinal irritation and pain.

The Army's recommended standards for lewisite in field drinking water were proposed on the basis of developmental toxicity studies in rats and rabbits administered lewisite by gavage. The NOELs in rats and rabbits were estimated to be 1.5 mg/kg and 0.016 mg/kg of body weight per day, respectively. Therefore, the lowest NOEL—0.016 mg/kg/day

(or 16 μg/kg/day) in the rabbit developmental toxicity study—was selected to derive the field drinking-water standards for lewisite. The arsenic fraction in 16 μg of lewisite is 5.8 μg. Based on a NOEL of 5.8 μg/kg/day, the Army proposed standards for arsenic (in lewisite) of 80 μg/L and 27 μg/L, assuming a water consumption of 5 L/day and 15 L/day, respectively.

The subcommittee concludes that the Army's proposed standards for lewisite (based on its arsenic fraction) are appropriate. Therefore, the subcommittee's recommended field drinking-water guidelines for lewisite are the same as the Army's proposed standards.

At present, there is no field drinking-water monitoring capability that can reliably detect lewisite or elemental arsenic at the recommended field drinking-water guidelines. Therefore, the subcommittee recommends that field monitoring techniques for low-level detection of arsenic or lewisite be developed.

CYANIDE

Cyanide has been known as a potent toxicant for over 200 years. Hydrogen cyanide gas was used as a CW agent by France during World War I. Typical symptoms of acute exposure of humans to sublethal doses of cyanide are headache, nausea, weakness, palpitations, tremors, and breathlessness. The nervous and respiratory systems are the first to fail in severe cyanide poisoning. When exposure is sufficiently high, death results from respiratory arrest.

The mechanism of cyanide toxicity involves inhibition of enzymes for cellular respiration. Blood cyanide concentrations have been correlated with various health effects. The most reliable data are the measured concentrations of cyanide in blood drawn from patients who received infusions of sodium nitroprusside (a cyanide-releasing drug) during surgery. On the basis of those data, a blood cyanide concentration of 0.5 mg/L is considered nontoxic. By using a pharmacokinetic model and assuming that the blood cyanide concentration of 0.5 mg/L is nontoxic, the Army proposed field drinking-water standards for cyanide of 2 mg/L and 6 mg/L, assuming a water consumption of 15 L/day and 5 L/day, respectively. The subcommittee is in agreement with the Army's proposed standards. Therefore, the subcommittee's recommended field

drinking-water guidelines for cyanide are the same as the Army's proposed standards.

CONCLUSIONS

Table E-1 summarizes the subcommittee's recommended field drinking-water guidelines for BZ; organophosphorus nerve agents GA, GB, GD, and VX; sulfur mustard; T-2 toxin; lewisite; and cyanide.

The Army has indicated that it plans to submit the subcommittee's recommended field drinking-water guidelines for the CW agents to a triservice (Army, Navy, and Air Force) medical review panel for formal adoption. If adopted, they will be used to develop joint service standards. These field drinking-water standards might then be submitted for incorporation into the North Atlantic Treaty Organization's Standardization Agreements and the Quadripartite Standardization Agreements.

TABLE E-1 Summary of the Subcommittee's Recommended Field Drinking-Water Guidelines for Selected CW Agents in Field Drinking Water[a]

	Recommended Guidelines	
CW Agent	5 L/day	15 L/day
BZ (μg/L)	7.0	2.3
Organophosphorus nerve agents		
Agent GA (μg/L)	70.0	22.5
Agent GB (μg/L)	13.8	4.6
Agent GD (μg/L)	6.0	2.0
Agent VX (μg/L)	7.5	2.5
Sulfur mustard (μg/L)	140.0	47.0
T-2 toxin (μg/L)	26.0	8.7
Lewisite (μg/L) (arsenic fraction)[b]	80.0	27.0
Cyanide (mg/L)	6.0	2.0

[a]Assumes a water consumption of up to 7 days.

[b]Based on detection of the arsenic fraction of lewisite in water; the corresponding concentration of lewisite is about 2.75 times greater.